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THE PHYSIOLOGY OF ANAPHYLACTIC "SHOCK" IN THE DOG.*†

RICHARD M. PEARCE,
Professor of Pathology
AND
ARTHUR B. EISENBREY,
Instructor in Pathology,
The University and Bellevue Hospital Medical College, New York.
(*From the Carnegie Laboratory of New York University.*)

THE investigation here presented was incidental to a study of the treatment of various experimental conditions of low blood pressure,[1] one of which was that associated with anaphylaxis in the dog. As a knowledge of the mechanism of the various forms of low pressure was essential to treatment, extensive physiological studies were made, and as the results of the study of anaphylactic shock are striking and have a very definite bearing on the problems of anaphylaxis in general, they are, therefore, made the subject of this communication.

Physiological and pharmacological studies of anaphylaxis are few in number and with the exception of the work of Arthus on the rabbit and Biedl and Kraus on the dog are limited to the guinea-pig. The general opinion[2] has been that the underlying cause is a change in the cells of the central nervous system and this view has had some support from the observations of Besredka, who found that the clinical manifestations of anaphylaxis could be lessened by ether anesthesia, and of Banzhaf and Famulener, who found a hypnotic dose of chloral hydrate would prevent symptoms in sensitized animals. The observations of these writers are, however, somewhat contradictory, and Rosenau and Anderson state that altho ether anesthesia may mask the symptoms, it does not prevent death.

Attempts to demonstrate specific anatomical lesions have been most unsatisfactory. Gay and Southard state that "we have to

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[1] R. M. Pearce and A. B. Eisenbrey, "A Study of Experimental Conditions of Low Blood Pressure of Non-Traumatic Origin," *Archives of Internal Medicine*, 1910 (in press).

[2] For the general literature of anaphylaxis, see the recent excellent summary by J. F. Anderson and M. J. Rosenau, *Archives of Internal Medicine*, 1909, 3, p. 519.

deal with an intimate cell reaction, demonstrable by definite cell lesions." They describe hemorrhages in the gastric mucosa and fatty changes in voluntary muscle, heart muscle, and nerve fibres. These observations have been confirmed in detail by Tscharnotzky.[1] The respiratory disturbance has been especially studied, first by Gay and Southard and lately by Auer and Lewis. The former consider the cause of death to be respiratory; respiration ceases in the inspiratory phase with gross and microscopic evidence of emphysema. A striking feature is severe diaphragmatic spasms. Rosenau and Anderson state, in view of the persistence of the heart beat after failure of respiration, that death is due to an effect on the nervous control of respiration. Auer and Lewis[2] conclude that anaphylactic death is due to asphyxia produced apparently by a tetanic contraction of the smooth muscle of the bronchioles. This contraction gradually occludes the lumen of the bronchioles and finally no air enters or leaves the lung, and in spite of evident respiratory efforts, the animal is strangulated. The lungs are distended in an inspiratory position and do not collapse when the chest is opened. The condition is due to a peripheral action, for destruction of spinal cord and medulla in no way affects the occurrence of the condition of the lung. Auer and Lewis do not care to give an opinion as to whether the toxic dose exerts its effect on the bronchial muscles alone or upon the vagus motor endings, or both. They also describe an initial rise in blood pressure, with later a gradual drop to 10 to 20 mm. of mercury or less, within 10 minutes. Heart block, probably due to asphyxia, also develops. Auer and Lewis also make the interesting observation that the administration of atropin, which paralyzes the bronchial muscles, causes a relaxation of the rigid anaphylactic lung, and that if atropin is given before the toxic dose of horse serum the pulmonary symptoms may be greatly reduced or prevented entirely. Anderson and Schultz[3] confirm most of these observations, but find that the administration of chloral hydrate, urethrane, adrenalin, and pure oxygen also may prevent the death from asphyxia. When life is thus prolonged, death results from the condition of low blood pressure.

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[1] "Travail de l'Institut Bact. de Moscow, 1909," *Ref. Bull. de l'Institut Pasteur*, 1909, 7, p. 591.

[2] *Jour. Amer. Med. Assoc.*, 1909, 53, p. 458; also *Jour. Exper. Med.*, 1910, 12, p. 151.

[3] *Proc. Soc. Exper. Biol. and Med.*, 1909, 7, p. 32.

Arthus,[1] who has worked with the rabbit, describes a very striking fall in blood pressure with polypnea, involuntary evacuation of feces and suppression of urine.

Anaphylaxis in the dog has not been extensively studied. This is possibly due to the negative results of Remlinger, and in part also to the fact that the phenomena in the dog differ in some respects from those in the guinea-pig. The chief differences are (1) the absence in the dog of the respiratory disturbance so characteristic in the guinea-pig and (2) the occurrence in the former animal of a fall in blood pressure which is more striking than that in the guinea-pig. The fall in blood pressure in the dog is considered by Biedl and Kraus[2] who first described it, to be the essential phenomenon of anaphylactic shock and to be due to a primary peripheral vaso-dilatation. These conclusions we have confirmed in an earlier communication.[3]

That the phenomena following an injection of horse serum into dogs previously sensitized with the same serum are to be considered as manifestations of anaphylaxis is shown by the following observations:

1. The intravenous injection of horse serum into a normal dog produces no clinical symptoms and no change in blood pressure.
2. An intravenous injection into a conscious animal three weeks after a subcutaneous injection of the same serum produces the following clinical manifestations:

Dog 50, weighing 4,680 gm., received 5 c.c. of normal horse serum subcutaneously on February 26. Twenty-three days later (March 21) 5 c.c. of the same serum were injected slowly into a superficial vein of the left hind leg under local anesthesia. Before the entire amount was injected, the animal became restless, and made retching movements. This was followed within two minutes by vomiting and involuntary evacuation of feces and urine. During this period, the animal when placed on the floor took a few steps, slowly and with a peculiar stiff-legged gait. At the end of three minutes it fell to the floor slowly and lay on its side with head prone. Retching movements continued. Respiration was somewhat deep and labored and 28 per minute as compared with 36 per minute before injection, no dyspnea; the pulse in the femoral artery could not be felt; superficial reflexes normal. Vomiting and involuntary defecation and micturition continued more or less intermittently for seven minutes after injection. The animal when placed upright could not stand, but this appeared to be due to muscular weakness rather than to paralysis; was indifferent to surroundings but entirely conscious. At the end of 22 minutes the pulse was palpable in the femoral; the animal could stand alone but preferred to lie down; though 10 minutes later it got up an walked around but was still weak. This degree of recovery occurred about half an hour after injection, and after the lapse of an hour the respirations were 28 per minute, the pulse readily palpable, the animal was weak but had power of locomotion, slight diarrhea was present, and the dog refused food. On the following morning he was found dead, a period of less than 15 hours having elapsed since injection. The cage showed evidence of profuse bloody diarrhea.

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[1] *Arch. Internat. d. Phys.*, 1909, 7, p. 471.

[2] *Wiener klin. Wchnschr.*, 1909, 22, p. 363.

[3] R. M. Pearce and A. B. Eisenbrey, *Proc. Soc. Exper. Biol. and Med.*, 1909, 7, p. 30.

Autopsy: No excess of fluid was found in the peritoneal and pleural cavities, the serous surfaces were smooth. The bladder contained a small amount of clear yellow urine. The intestines appeared somewhat dark in color and the lower 15 cm. of the rectum showed numerous pin head petechial spots beneath the peritoneum; larger ecchymotic areas occurred beneath the serosa of the gall bladder. Spleen, liver, and kidneys appeared normal. In the greater curvature of the stomach the mucosa over two areas of about 1.5 cm. in diameter was intensely hemorrhagic and swollen and some superficial erosion of the epithelium was evident. In the region of the pylorus both the stomach and duodenum were normal, but about 2 cm. below the pylorus and for a distance of 27 cm. along the small intestine, the mucosa was greatly swollen and hemorrhagic. Below this area the Peyer's patches were elevated and dark colored, but hemorrhages were absent. A few centimeters below the ileocaecal valve the colon was intensely hemorrhagic with considerable erosion of epithelium. The mucosa of the gall bladder was smooth and showed no hemorrhage. Heart and lungs appeared normal; the latter collapsed on opening the thorax and presented some hypostatic congestion in dependent parts. The brain showed no macroscopic lesions.

3. In animals under complete ether anesthesia the objective manifestations of anaphylactic shock are absent;[1] in all such, however, an immediate and prolonged fall in blood pressure which persists for a considerable time occurs. This has been seen in 40 of 42 animals; in two dogs with pneumonia (distemper) it failed to occur. The lowered pressure is unaccompanied by noteworthy respiratory or cardiac disturbance.

4. After anaphylactic shock has been produced in a sensitized animal and the animal has recovered from the acute manifestations, subsequent injections fail to cause a reaction evident either by clinical symptoms or by change in the blood pressure.

These results, which are in accord with those of Biedl and Kraus, indicate that the principles underlying anaphylaxis in the dog are the same as those for anaphylaxis in the guinea-pig.

We have regarded the fall in blood pressure as the constant and most characteristic phenomenon of anaphylactic shock in the dog, and have based our conclusions concerning the physiology of anaphylaxis on its presence or absence under various experimental conditions.

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[1] Vomiting, involuntary defecation and passage of urine, have been observed once in an animal anesthetized by Gréhant's method.

The first experiments had for their object the determination as to whether the condition of low blood pressure was due to changes in the blood caused by the injection of the toxic dose or to changes in the fixt cells. It has been generally assumed in all recent investigations with the guinea-pig that the latter explanation is the correct one, but as far as we are aware this has never been determined by transfusion experiments such as we employed. Furthermore, Biedl and Kraus show that not only is there a change in the numerical relation of the two types of cells of the blood one to another, but also, and this we have confirmed, that a decreased coagubility of the blood occurs. It seemed important, therefore, to rule out at once the influence of possible primary or secondary toxic bodies formed in the circulating blood by the union of the bodies in the toxic dose of serum with those bodies which might be formed in the blood of the animal by the first injection.

Our procedure has been to exsanguinate, under ether anesthesia, a small normal dog (A) and to transfuse this animal by Crile's method with the blood of a larger sensitized dog (B) until the blood pressure reached approximately its original level. After sufficient blood has been obtained from B to raise the pressure of A, the sensitized dog is then bled to exsanguination and transfused from a third normal dog (C) until its pressure reaches its previous normal level. At the proper moment, the normal dog containing the blood of the sensitized dog, and the latter containing the blood of the normal dog, each receives intravenously the toxic dose of horse serum. In the former, a fall in pressure does not occur and in the latter it does, thus proving that the phenomenon of anaphylaxis is due to a reaction in the fixt cells and not either primarily or secondarily to changes in the blood. This result is in accord with the contention of Gay and Southard and of Friedberger that the reaction of intoxication in the guinea-pig is located within the body cells and is opposed to the theory of "antibodies."[1]

The following protocol, presented briefly, is illustrative:

Dog A, weight 6,260 gm., ether anesthesia, cannula in femoral artery, connected with mercury manometer and recording on a kymograph. Original pressure 92 mm. Bled from the carotid artery until no more blood flowed, the pressure dropping to

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[1] Compare with views of Friedberger, *Ztschr. f. Immunitätsforsch. u. exper. Therap.*, 1909, 2, p. 208; 1909, 3, p. 581; 1910, 4, p. 612, and Friedemann, *ibid.*, 1909, 2, p. 591.

16 mm. Hg. Transfused from B for 17 minutes by carotid anastomosis, until pressure reached original level, when 5 c.c. of normal horse serum were injected into the femoral vein. No change in pressure except slight mechanical rise.

Dog B (No. 17), weight 8,020 gm. Had received 5 c.c. horse serum subcutaneously 25 days before. Ether anesthesia. Arrangement of cannula as in A. Original blood pressure 90 mm. After transfusion sufficient to raise pressure of A, animal B was bled for 16 minutes until flow ceased, when blood pressure was at a level of 14 mm. Transfusion from dog C was then begun and continued for 24 minutes when permanent level equal to previous normal level was obtained. At this time 5 c.c. horse serum were injected into the femoral vein with an immediate fall in pressure to 24 mm Hg.

Dog C, normal dog, weighing 9,100 gm., prepared as were A and B, and used for transfusion of B.

Having thus determined that the reaction was evidently due to an effect on the fixt cells of the body and presumably on those of the vasomotor system, the question of the general distribution of the blood in anaphylactic shock was studied as a preliminary to the study of peripheral and central influence. For this purpose, experiments were made under the following conditions:

All animals were under full ether anesthesia. The blood pressure was taken from the left femoral artery with a mercury manometer. Injections were made into the right saphenous vein. The changes in blood distribution were determined by oncometric studies by means of guttapercha capsules applied to spleen, kidney, and intestine, by a cannula introduced into the right common iliac vein and projecting into the inferior vena cava, by plethysmographic study of a forelimb and by a metal cylinder penetrating into the cranial cavity. Each of these was connected by rubber tubing with a bellows recorder allowing simultaneous records on a revolving drum. It was thus possible in a single experiment to obtain simultaneously, as was frequently done, records of volumetric changes in the femoral artery, iliac vein, kidney, spleen, and intestine, with also a record of the respiration, or any combination of these with a record of variation in a limb or in intracranial pressure.

The temperature of the animal was maintained by the use of a hotwater coil encircling the greater part of the trunk and a record of changes in temperature was obtained by a thermometer in the rectum. Normal horse serum was used in doses of 5 c.c., subcutaneously for sensitization, and the physiological experiment was made after about 21 days. The dose used to bring about anaphylactic "shock," usually 5 c.c., has varied from 2 to 6 c.c., altho it must be admitted that no attempt has been made to determine the minimal toxic dose. It has always been given intravenously.

The study of blood distribution included six observations. The fall in arterial pressure, as well as the change in the volume of the kidney, and the character of the respiration, are shown in Fig. 1.

It is apparent that anaphylactic shock is characterized by an abrupt fall of blood pressure averaging 50 to 70 mm. Hg which is independent of initial change in heart action, tho during the continuance of low pressure the amplitude of the pulse wave is greatly diminished, the result presumably of the small amount of blood reaching the heart. Respiratory disturbances, except in as far as they occur as a result of medullary anemia due to the low general arterial pressure, are absent. Oncometric studies show a decrease in the volume of kidney, intestine, and spleen simultaneously with the decrease in arterial pressure. Of these three organs the decrease is, as a rule, most marked in the kidney and least in the intestine. A very slight initial decrease in brain volume has been found as well as a slight diminution in the volume of an extremity. This decreased peripheral circulation is accompanied by an accumulation of blood in the liver and large veins of the abdomen. This has been determined by inspection of the liver and large veins and by the observation that a cannula introduced into the inferior vena cava and connected with a water manometer shows a moderate increase of pressure, equal to 6 to 10 mm. water, at the time of the fall in arterial pressure, with an almost immediate return to normal level as the blood becomes evenly distributed throughout the large venous trunks.

It is evident, therefore, that the important feature of the condition of low pressure here described is a lack of tone of the vessels, particularly of the splanchnic area, characterized by extreme venous congestion from which the animal does not quickly recover. It is essentially the condition characterized as a "bleeding into the veins of the abdomen" and in many respects is analogous to the circulatory disturbance of surgical shock.

The next step, naturally, was to determine to what extent this condition was due to peripheral and to what extent to central vasomoter disturbances. To determine the influence of the central

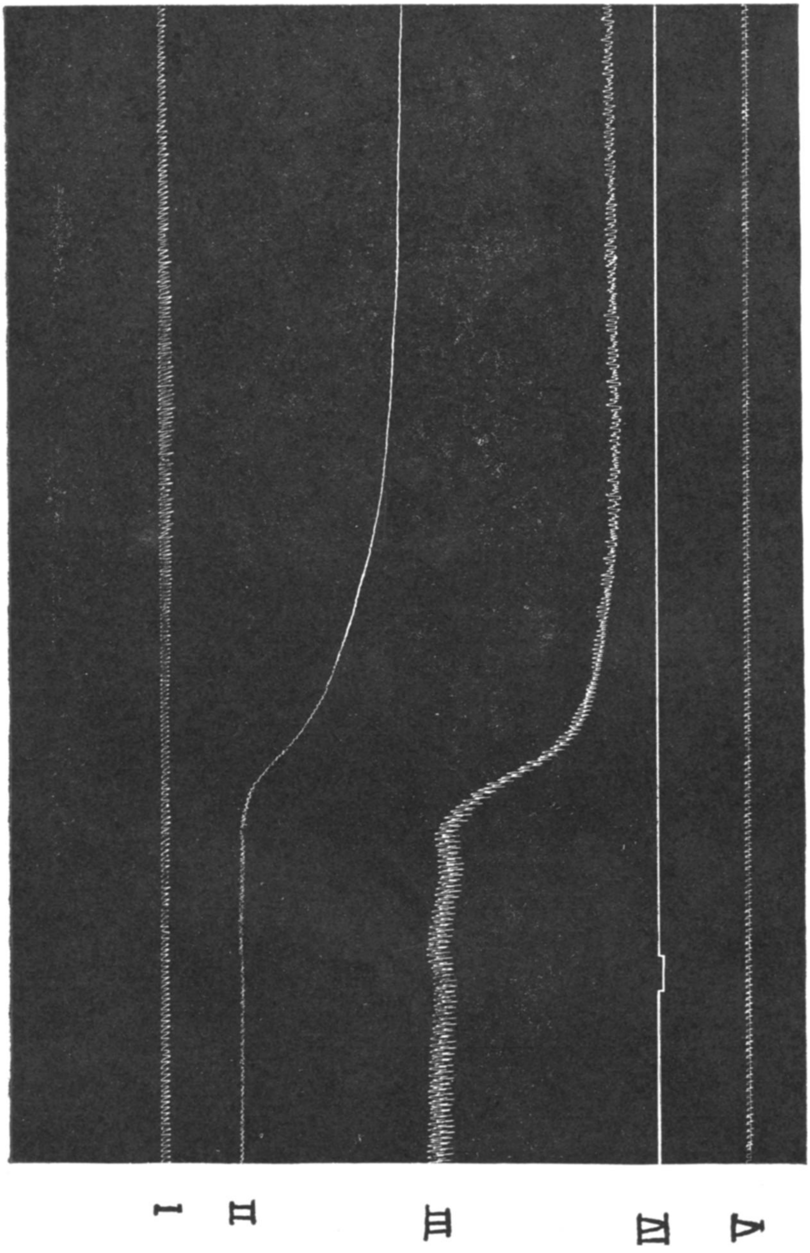

FIG. 1.—This tracing illustrates the effects of the injection of 5 c.c. normal horse serum into the saphenous vein of a dog (weight 838 ograms, that had been given 5 c.c. of the same serum 22 days before. Ether anesthesia. I=respiration; II=kidney volume (oncometer on left kidney); III=blood pressure; IV=base line with signal at time of injection; V=time in seconds.

mechanism, experiments were done under ether anesthesia, in which the spinal cord, vagi, cervical sympathetic and splanchnic nerves were severed. None of these procedures, singly or collectively, prevented the fall in pressure, thus pointing to the absence or slight importance of central influence. Such evidence, tho usually considered conclusive by physiologists, we preferred not to accept without absolutely excluding the influence of centers in the cord as well as the secondary effect of cerebro-medullary anemia. Three groups of experiments were therefore performed. These included the study of anaphylaxis under the following conditions: (1) decapitation, (2) decapitation and destruction of the cord with blood pressure reinforced by transfusion, and (3) with the cerebral circulation independent of the circulation of the body. All experiments of these three groups were done under complete ether anesthesia by tracheal cannula.

1. The object of decapitation[1] was naturally to eliminate all cerebro-medullary influence. After this procedure, it was found that the blood pressure falls to a point about one-half of its original level and remains there with little variation, if care is exercised to keep the artificial respiration uniform and to maintain the body heat, for a period covering the usual duration of the experiments. With the loss of vagus influence the heart rate is quickened and the excursions of the pulse wave shortened. The respiratory curve in the blood pressure tracing is well marked. With these conditions prevailing the toxic dose of horse serum caused a fall of blood pressure to the level occuring from similar doses in intact animals. The onset of the fall was less abrupt and the low level was reached more slowly. That the fall could occur, however, independently of cerebro-medullary influence was clearly shown.

2. In the experiments in which the cord was mechanically destroyed after decapitation, the object was to eliminate all except local vasomotor influences. After destruction of the cord it was found that a further dilatation and fall in blood pressure occurs beyond that caused by the decapitation and that death rapidly ensues. This is apparently due to the fact that with the additional loss of the spinal con-

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[1] Decapitation may be performed with a comparatively negligible amount of hemorrhage and therefore with but slight effect on the circulation of the trunk, by clamping the common carotid arteries and the internal and external jugular veins simultaneously low in the neck, having first ligated the vertebral arteries at the point where they enter their canals in the transverse processes of the cervical vertebrae.

strictor influence an insufficient volume of blood reaches the heart. By means of transfusion, however, it was possible to raise the blood pressure and maintain the circulation at a point permitting manometric record of further change in the pressure, and under such circumstances it is found that the injection of horse serum into a sensitized dog causes a definite fall in pressure, demonstrating conclusively that the essential phenomenon of anaphylaxis may be brought about independently of the cerebro-medullary and the spinal centers.

3. While the experiments on decapitated animals and on those with spinal cord destroyed and with vagi and cervical sympathetic nerves severed have shown that the usual effect on the blood pressure may be produced independently of the central action, such experiments have not of course shown that the central vasomotor mechanism does not perhaps play some part in the symptom complex presented by intact animals.

With the object of ascertaining the possibility of a central action in anaphylaxis, without the complication of the known peripheral effects, we were obliged to devise a means by which the horse serum might be introduced into the cerebral circulation, but not reach the circulation of the body. For this purpose a special operation was perfected, the details of which are described elsewhere,[1] whereby all vascular communication between the trunk and head was obliterated and the circulation in the head and neck maintained independently by transfusion from the carotid artery of a normal animal, the outflow from the recipient being through a free opening in the external jugular vein. Following a short period of irregularity due to the temporary changes in the cerebral circulation incidental to the technic of isolation, the general blood pressure of the recipient is maintained at a normal level, and horse serum may be introduced into the cerebral or into the peripheral circulations exclusively without any of the injected material reaching the circulation of the other portion of the animal.

When, under such circumstances, horse serum is introduced through the anastomosing carotid artery into the cerebral circulation of a sensitized animal, a slight transient lowering of the blood pressure is produced, but it is not the typical depression of anaphylactic shock in intact animals. The action is prompt, but the depression, to give the figures in one experiment, is only 16 mm. Hg with return to normal level in 23 seconds. If, some minutes after recovery from this effect, the serum is injected into the circulation of the trunk, it produces a lowering of the blood pressure to a level which corresponds to that in the typical condition of anaphylactic shock in the intact animal, for example, in the experiment quoted a fall of 74 mm. Hg with the low level persisting.

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[1] A. B. Eisenbrey, *Proc. Soc. Exper. Biol.*, 1910, 7 (in press).

In view of the well-known fact that when anaphylactic shock is once produced further injections of the serum have no effect, the results in the above experiments show not only the completeness of the isolation of the cerebral circulation from that of the trunk but also that the peripheral influence is the essential factor in the production of the change in blood pressure so characteristic of anaphylaxis.

It was apparent, therefore, that the action was in the largest degree peripheral, either on the nerve endings or on the muscle of the vessels themselves, which is in accord with the observations of Biedl and Kraus concerning the influence of barium chloride in modifying the blood pressure phenomena of anaphylactic shock.

A number of pharmacological experiments were then made to still further localize the action. These are based on the experiments of Dixon[1] and Brodie and Dixon[2] with apocodeine. This substance in very large doses paralyzes vasomotor nerve endings; and "when its action is complete pilocarpine, physostigmine, and adrenalin have no effect on the blood vessels or blood pressure, whilst barium and digitalis will still constrict the blood vessels and raise blood pressure. The first three drugs, it is therefore assumed, act on nerve endings and the latter two directly on muscle."

As the low pressure of anaphylaxis both in its level and in permanence resembles closely that due to apocodeine we have tested the effect of adrenalin and barium in the hope of finding analogous mechanisms. The results are not conclusive. While barium causes an increase in pressure,[1] adrenalin does likewise; the latter, however, is but slight and never equal, even if percentile values are considered, to the normal adrenalin reaction. Assuming therefore that adrenalin acts through the nerve endings, it is evident that in anaphylactic shock altho these structures are not completely paralyzed, their activity is greatly diminished not only as shown by the slight adrenalin action but also by the fact that splanchnic stimulation causes a smaller rise in pressure than in the normal animal. Nitroglycerin, which according to Dixon and Brodie acts only on the vessel muscle, also causes a further fall in pressure, as does also to a slight extent dog's urine, which as we have shown elsewhere,[2] apparently lowers blood pressure by an action on the nerve endings. It is therefore evident that altho this condition of low pressure is due in greatest part, at least, to a disturbance of the peripheral vasomotor mechanism, it is not possible to say that the function of either the nerve endings or the muscle is completely in abeyance. The pharmacological experiments indicate, however, that the nerve endings bear the brunt of the injury. This view is supported by experiments with apocodeine. If a sensitized dog under the influence of apocodeine received an injection of serum, a further depression of the circulation was not obtained. In fact, the blood pressure was raised a few millimeters by the mechanical effect of the injection and remained so for a period of about one minute, gradually returning to a point slightly below the original level after two minutes.

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[1] *Jour. of Physiol.*, 1903, 30, p. 97.

[2] *Ibid.*, p. 476.

[1] We have also confirmed the observation of Biedl and Kraus that the administration of barium chloride to a sensitized animal before giving the toxic dose modifies or prevents the characteristic fall in pressure.

SUMMARY

1. Anaphylaxis in the dog is characterized subjectively by a sudden and persistent fall in blood pressure followed by objective symptoms referable to cerebral anemia.
2. Exsanguination and transfusion experiments demonstrate that the disturbance is due to a reaction in the fixt cells and not to changes occurring primarily or secondarily in the circulating blood.
3. Experiments in which the peripheral and central vasomotor mechanisms have been separated by various methods (section, decapitation, destruction of the cord, and isolated circulation) show that the chief influence is exerted on the peripheral vaso-motor system.
4. Pharmacological experiments point to an influence on the nerve endings rather than to one on the muscle of the vessels.

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[2] *Amer. Jour. of Physiol.*, 1910, 26, p. 26.